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Review

Phenazepam: The drug that came in from the cold

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ABSTRACT

In the past few years there has been concern in Western Europe and in the US about the rise in abuse of phenazepam, a benzodiazepine that was originally developed in the USSR in the mid- to late 1970s.[1–4] Although phenazepam is one of the most widely prescribed benzodiazepines in Russia and other commonwealth of independent state (CIS) countries, it has not been licensed elsewhere in the world. Due to very limited licensed geographical distribution, there is very little peer-reviewed literature that is not written in Russian. In this article, we review the current state of what is currently known about phenazepam. This information on phenazepam and how it can be detected in biological specimens should assist the forensic community in identifying phenazepam in routine toxicology screening and interpreting any phenazepam concentrations that are obtained.

1. Introduction

Phenazepam [7-bromo-5-(2-chlorophenyl)-1, 3-dihydro-2H-1,4-benzodiazepine-2-one], sometimes called fenazepam (Fig. 1A), is part of the 1,4-benzodiazepine group of benzodiazepines along with drugs such as diazepam, nordazepam, oxazepam and temazepam. It is however one of very few of the 1,4-benzodiazepine group to contain a bromine atom, along with the active form of gidazepam, another soviet-developed benzodiazepine[5] and bromazepam. As with other benzodiazepines, it is used clinically for its anxiolytic, anticonvulsant, muscle-relaxing and sedating properties,[6] and is available as 0.5-mg and 1-mg tablets,[6] injectable solutions (0.1%, 0.3%) or transdermal patches (Phenopercuten).[7] Clinically the dose of phenazepam that is given depends on what condition is being treated but does not exceed 10 mg day^{-1}, and is usually not more than 5 mg day^{-1}. Illicitly, phenazepam has been reported being sold as a powder, tablets, in the USA, spiked in lysergic acid diethylamide (LSD) mimic blotters[8,9] and in New Zealand phenazepam has been found in a synthetic cannabinoid mix called 'Kronic'.[10] Reported recreational doses of phenazepam are around 2–10 mg, but sometimes more.[8]

2. Pharmacokinetics and metabolism of phenazepam

2.1. Pharmacokinetics

There is limited information on the pharmacokinetics and metabolism of phenazepam in humans. After oral dosing with 3 mg or 5 mg, phenazepam has a peak plasma concentration between 200 and 400 μg l^{-1} at approximately 4 h; the drug was eliminated slowly with a $T^{1/2}$ of about 60 h.[11] However, this is in contrast to a study where epileptic patients were given either an intramuscular or an intravenous injection of 2-mg phenazepam where the $T^{1/2}$ was estimated to be between 14.9 and 15.6 h.[12] These studies suggest that the $T^{1/2}$ could be between 15 and 60 h, but more work will need to be carried out in order to give a more precise $T^{1/2}$. The same study into epileptic patients investigated repeated injections of 1-mg phenazepam, this showed that the constant steady state (Css) plasma concentration was ~157 μg l^{-1}, with an estimated bioavailability of 80%.[11] Although studies on humans have shown that the (*Vd*) of phenazepam is 4.7–6.0 l,[12] the weight of the patients was not given, so these results are difficult to compare with the *Vd* of other benzodiazepines in humans (diazepam 0.7–2.6 l kg^{-1}; temazepam 0.8–1.0 l kg^{-1}; and oxazepam 0.7–1.6 l kg^{-1}), but it would be expected that as with other benzodiazepines phenazepam would exhibit post-mortem redistribution complicating interpretation of post-mortem levels of phenazepam.[13] The pharmacokinetics of phenazepam discussed in this section are summarised in Table 1.

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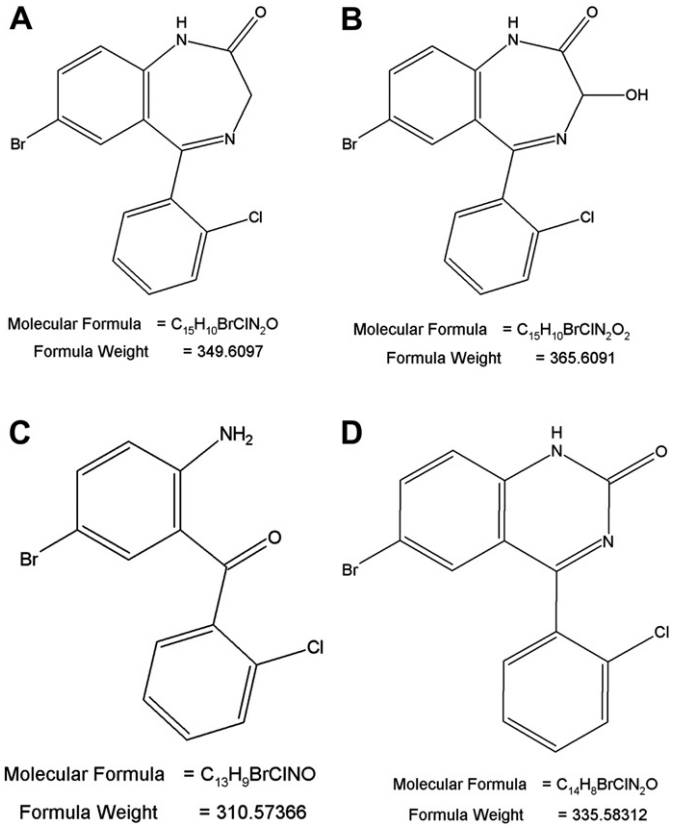

Fig. 1. Chemical structures of (A) phenazepam and its metabolites; (B) 3-hydroxy-phenazepam; (C) 5-bromo-(2-chlorophenyl)-2-aminobenzophenone (ABPH) also known as 2-amino-5-bromo,chloro-aminobenzophenone (ABCB); and (D) 6-bromo-(2-chlorophenyl) quinazoline-2-one (QNZ).

The pharmacokinetics of phenazepam in animals are beyond the scope of this review but further information can be found in the following publications: Refs. 14–17.

2.2. Metabolism

The metabolism of phenazepam appears to follow similar metabolic routes to many other benzodiazepines with a hydroxylated metabolite, 3-hydroxy-phenazepam (Fig. 1B),[11] a hydrolysed metabolite 5-bromo-(2-chlorophenyl)-2-aminobenzophenone (ABPH), also known as 2-amino-5-bromo,chloro-aminobenzophenone (ABCB;, Fig. 1C),[18,19] as well as another metabolite 6-bromo-(2-chlorophenyl) quinazoline-2-one (QNZ), (Fig. 1D). There may also be glucuronides of some of the metabolites, as these have been found in rat studies.[17] Limited information is available about the prevalence of the various metabolites in humans. A study in which a 5-mg oral dose of phenazepam was given to healthy volunteers resulted in 3-hydroxy-phenazepam being detected in the urine but not in blood samples.[11] ABPH has been detected in blood, urine, liver and kidney post-mortem samples of a suspected fatality due to phenazepam.[19] Based on information from other benzodiazepines, it is likely that the hydroxylation of phenazepam is catalysed by the cytochrome P450 family specifically CYP3A.[20]

Table 1
Summary of the pharmacokinetics of phenazepam in humans.

Parameter	Value	Dose/route	Reference
Volume of Distribution (*Vd*)	4.7–6.0 L	3 or 5 mg (oral)/ 2 mg (iv or im)	11,12
Half-life ($T^{1/2}$)	~15–60 h	3 or 5 mg (oral)/ 2 mg (iv or im)	11,12
Bioavailability	80%	2 mg (iv or im)	11
C_{max}	200–400 μg/L	3 or 5 mg (oral)	11
T_{max}	~4 h	3 or 5 mg (oral)	11
Elimination rate constant (K_{el})	0.044–0.047	2 mg (iv or im)	12
Plasma clearance (Clp)	220.4–267.9 ml/h	2 mg (iv or im)	12
Constant Steady State (Css)	157.2 μg/L	Repeated 1 mg iv	12

3. Pharmacology of phenazepam and its metabolites

3.1. Pharmacodynamics

Pharmacologically both phenazepam and 3-hydroxy-phenazepam have been described as full γ-aminobutyric acid type A ($GABA_A$) receptor agonists[17,21] and both appear to be pharmacologically active with greater potency than diazepam probably due to the bromine atom in the molecule. The two other metabolites of phenazepam, QNZ and ABPH, also appear to have pharmacological activity, at least in *in vitro* experiments. QNZ and ABPH exhibited biphasic effects at the $GABA_A$ receptor initially potentiating GABA responses at low concentrations and then inhibiting them at higher micromolar concentrations; however, these metabolites are only likely to have significant *in vivo* pharmacological effects in overdose situations.[17,21] ABPH is also thought to act at both glycine and *N*-methyl-D-aspartate (NMDA) receptors again at high micromolar concentrations.[22]

3.2. Clinical pharmacology and potency of phenazepam

Clinically phenazepam has been described by illicit users as being more potent than diazepam with 1 mg of phenazepam being the equivalent of up to 10 mg of diazepam.[23] The greater potency of phenazepam is borne out by both *in vivo* studies, in which phenazepam was found to elicit a more pronounced and more lasting tranquilising effect as compared to that of diazepam in a double-blind trial of patients about to undergo surgery,[24] and *in vitro* studies on rat cerebellar slices in which both phenazepam and 3-hydroxy-phenazepam potentiated GABA responses with EC_{50}'s of 6.1 nM and 10.3 nM, respectively, compared to the EC_{50} of diazepam (13.5 nM).[21]

4. Phenazepam blood levels and side effects

4.1. Sources of information on phenazepam

In the literature there is one report of a fatality due to phenazepam alone,[19] one report of a fatality due to phenazepam and poppy seed tea[3] and one report of a phenazepam fatality in combination with opiates.[25] Phenazepam intoxication has been reported in both adults[26] and children.[27] There are also numerous reports of the detection of phenazepam in drivers killed in road accidents,[4] apprehended drivers,[2,28] post-mortem cases[29] and a case of intoxication after endonasal consumption of a substance that the users thought was cocaine but was actually found to be a mixture of butylone, phenazepam and cocaine.[30]

4.2. Phenazepam side effects

Similar to other benzodiazepines, the most common side effects which have been reported are central nervous system (CNS) depression, impaired balance, slurred speech, confusion, memory loss, ataxia, muscle hypotonia, tachycardia (or bradycardia) and both auditory and visual hallucinations.[19,26,27,30,31] What was most noticeable with the consumption of phenazepam that was not encountered with other benzodiazepines was the long duration of side effects. In 61 cases that were reported in Sweden over a period

of 18 months, 14 (23%) of the 61 patients experienced symptoms more than 5 days after ingestion, with CNS depression lasting up to 3 weeks. Symptoms were also fluctuating which is also atypical in benzodiazepine poisoning.[27]

4.3. Paediatric phenazepam blood concentrations and side effects in poisoning cases

A systematic study of Russian children aged 11–14 who presented with phenazepam poisoning allowed the authors to compare the intoxication to blood levels of phenazepam. They concluded that 2.5–3.2 $\mu g\,l^{-1}$ characterised slight poisoning, 3.25–4.01 $\mu g\,l^{-1}$ medium severity poisoning and greater than 4.02 $\mu g\,l^{-1}$ severe poisoning. Table 2 gives detailed features of toxicity for the blood concentrations of phenazepam observed in this study.[27]

4.4. Adult phenazepam blood concentrations

In adults, the blood concentrations seen following recreational use of phenazepam have been obtained mainly from cases of driving under the influence of drugs (DUID). In Sweden, blood concentrations of 5–3000 $\mu g\,l^{-1}$ (median 98 $\mu g\,l^{-1}$) were observed in 86 cases. In four of these cases, aberrations/functional disorders found by clinical examination were found to be exclusively to be due to phenazepam. The blood concentrations in these four instances were 230–3000 $\mu g\,l^{-1}$.[2] These values are similar to those found in four DUID cases from the USA and 20 DUID cases from Finland in which blood phenazepam in CNS impaired drivers was found to be between 380 and 500 $\mu g\,l^{-1}$[28] and 18 and 400 $\mu g\,l^{-1}$,[32] respectively. In Norway, legal limits and impairment limits for phenazepam blood concentrations have been proposed as 1.8 $\mu g\,l^{-1}$ (comparable to 0.02% alcohol) for the legal limit, 5 $\mu g\,l^{-1}$ (comparable to 0.05% alcohol) low impairment limit and 10 $\mu g\,l^{-1}$ (comparable to 0.12% alcohol) high impairment limit. They have defined the legal limit as being one-fifth of the blood concentration typically seen after the administration of a recreational dose to a single naive individual. The levels of impairment are used for metering out sanctions in the Norwegian legal system.[4] In the Swedish case of acute overdose, the blood concentration of phenazepam was 1.2 $\mu g\,g^{-1}$ ($\sim$1200 $\mu g\,l^{-1}$) 7 days post-ingestion of an estimated 400–600 mg of phenazepam.[26]

4.5. Blood levels of phenazepam and its metabolites in deaths associated with phenazepam and in post-mortem samples

In the three cases reported in the literature in which phenazepam was implicated in fatalities only one involved phenazepam alone; a 32-year-old female was found dead surrounded by tablets of phenazepam, tablet remnants were found in the stomach contents. No phenazepam concentrations were reported. However, the concentration of ABPH (aka ABCB), a metabolite of phenazepam, was reported, blood 11,600 $\mu g\,l^{-1}$; urine 43 500 $\mu g\,l^{-1}$; stomach contents 362 $mg\,kg^{-1}$; liver 18.6 $mg\,kg^{-1}$; and kidney 23.9 $mg\,kg^{-1}$. In the second fatality, phenazepam, morphine, codeine and thebaine were detected in the blood at concentrations of 386, 116, 85 and 72 $\mu g\,l^{-1}$, respectively. The cause of death in this case was attributed to multidrug toxicity.[3] In the third case, the deceased had consumed phenazepam, together with other prescribed medication. Blood analysis revealed morphine (360 $\mu g\,l^{-1}$), codeine (380 $\mu g\,l^{-1}$) phenazepam (2520 $\mu g\,l^{-1}$) paracetamol (no concentration given) and olanzapine (no concentration given). The cause of death was ascribed to 'phenazepam, opiate and codeine toxicity'.[25] Phenazepam has also been detected in 19 post-mortem cases screened in the West of Scotland between 2009 and 2011; the concentrations reported were between 8 and 1200 $\mu g\,l^{-1}$. Although no drug concentrations were given for individual cases in the report, in two of the cases phenazepam was stated as a contributing factor in the case of death. In one, phenazepam was the sole cause of death.[29]

Table 2
Blood concentration of phenazepam and its associated features of toxicity in children aged 11–14. Adapted from Ref. 21.

Blood phenazepam concentration (μg/L)	Features of toxicity
2.50 ± 1.55	Somnolence, pupils of medium dimension, skin of usual colouring
2.65 ± 0.95	Initial ataxia
2.76 ± 0.98	Tachycardia, muscle hypotonia
3.25 ± 0.55	Soporific condition
4.02 ± 0.3	Coma

5. Detection and analysis of phenazepam in biological samples

During the analysis of the blood concentration for the above cases, various analytical methods have been used. Phenazepam can be detected in enzyme-multiplied immunoassay (EMIT) screens (positive result for concentrations $\geq$50 $\mu g\,l^{-1}$).[3,28] This initial result can be confirmed by GC/MS (LOQ 10 $\mu g\,l^{-1}$),[32] UPLC-MS (LOQ 5 $\mu g\,l^{-1}$)[3] LC-MS (LOQ 1 $\mu g\,l^{-1}$),[33] GC-FID (No LOQ given)[14] and GC-EI-MS (LOQ 20 $\mu g\,l^{-1}$).[34] We have also developed methods for the detection of phenazepam in HPLC-DAD and LC-MS (http://www.dundee.ac.uk/forensicmedicine/drugmonographs/). Only limited detection/quantitation methods for the metabolites of phenazepam have been published. ABPH (aka ABCB) can be identified using TLC and quantitated with GC-FID[19] and 3-OH-phenazepam can be quanititated by GC-MS (LOD 1 $\mu g\,l^{-1}$).[11,35]

6. Current legal status of phenazepam around the world

As of September 2011, the legal status of phenazepam is inconsistent worldwide. In the US it does not have Food and Drug Administration (FDA) approval, so cannot be marketed as a drug, but is not listed under the controlled substances act.[3] In Canada, the drug is not reported to be controlled. Phenazepam is not controlled at the European Union (EU) level; however, individual member states have put in measures to control it. In the UK, it is currently illegal to import phenazepam and it has been recommended by the advisory council on the misuse of drugs (ACMD) to be controlled.[36] It is controlled in the Republic of Ireland and in many eastern European nations such as Estonia, Latvia, Lithuania and Maldova and also in the Scandinavian countries of Norway and Sweden.[37]

7. Conclusions

Phenazepam is an emerging drug of abuse in Western Europe and the USA. It appears that it is more potent than the commonly abused benzodiazepine diazepam, and has more severe and longer-lasting side effects. It is expected that as with other benzodiazepines severe toxicity would be associated with concomitant use of other CNS depressant drugs, especially opiates and alcohol; however, recreational doses are likely to cause impairment of judgement especially when driving and operating machinery. The detection and quantitation of phenazepam in biological fluids can be carried out using standard laboratory techniques.

Conflict of interest

The authors have no conflicts of interest.

Appendix. Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jflm.2011.12.014.

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